Welcome to STN International! Enter x:x

LOGINID:ssspta1202sxq

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	Jun 03	New e-mail delivery for search results now available
NEWS 4	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 5	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS 6	Aug 26	Sequence searching in REGISTRY enhanced
NEWS 7	Sep 03	JAPIO has been reloaded and enhanced
NEWS 8	Sep 16	Experimental properties added to the REGISTRY file
NEWS 9	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS 10	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS 11	Oct 24	BEILSTEIN adds new search fields
NEWS 12	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 13	Nov 18	DKILIT has been renamed APOLLIT
NEWS 14	Nov 25	More calculated properties added to REGISTRY
NEWS 15	Dec 04	CSA files on STN
NEWS 16	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 17	Dec 17	TOXCENTER enhanced with additional content
NEWS 18	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS 19	Jan 29	Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC
NEWS 20	Feb 13	CANCERLIT is no longer being updated
NEWS 21	Feb 24	METADEX enhancements
NEWS 22	Feb 24	PCTGEN now available on STN
NEWS 23	Feb 24	TEMA now available on STN
NEWS 24	Feb 26	NTIS now allows simultaneous left and right truncation
NEWS 25	Feb 26	PCTFULL now contains images
NEWS 26	Mar 04	SDI PACKAGE for monthly delivery of multifile SDI results
NEWS 27	Mar 20	EVENTLINE will be removed from STN
NEWS 28	Mar 24	PATDPAFULL now available on STN
NEWS 29	Mar 24	Additional information for trade-named substances without structures available in REGISTRY
NEWS 30	Apr 11	Display formats in DGENE enhanced
NEWS 31	Apr 14	MEDLINE Reload
NEWS 32	Apr 17	Polymer searching in REGISTRY enhanced
NEWS 33	Jun 13	Indexing from 1947 to 1956 added to records in CA/CAPLUS
NEWS 34	Apr 21	New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX
NEWS 35	Apr 28	RDISCLOSURE now available on STN
NEWS 36	May 05	Pharmacokinetic information and systematic chemical names added to PHAR
NEWS 37	May 15	MEDLINE file segment of TOXCENTER reloaded
NEWS 38	May 15	Supporter information for ENCOMPPAT and ENCOMPLIT updated
NEWS 39	May 16	CHEMREACT will be removed from STN

NEWS 40 May 19 Simultaneous left and right truncation added to WSCA
NEWS 41 May 19 RAPRA enhanced with new search field, simultaneous left and right truncation
NEWS 42 Jun 06 Simultaneous left and right truncation added to CBNB
NEWS 43 Jun 06 PASCAL enhanced with additional data
NEWS 44 Jun 20 2003 edition of the FSTA Thesaurus is now available

NEWS EXPRESS April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 11:59:58 ON 24 JUN 2003

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'CAPLUS' ENTERED AT 12:00:11 ON 24 JUN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 24 Jun 2003 VOL 138 ISS 26
FILE LAST UPDATED: 23 Jun 2003 (20030623/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

09865859

```
=> s angiogenesis
L1       17499 ANGIOGENESIS

=> s l1 and inhibition
        671703 INHIBITION
L2        4010 L1 AND INHIBITION

=> s l2 and (PPAR receptor)
          3474 PPAR
        515855 RECEPTOR
           111 PPAR RECEPTOR
                 (PPAR(W)RECEPTOR)
L3           0 L2 AND (PPAR RECEPTOR)

=> s l2and PPAR
             1 L2AND
          3474 PPAR
L4           0 L2AND PPAR
                 (L2AND(W)PPAR)

=> s l2 and PPAR
          3474 PPAR
L5          14 L2 AND PPAR

=> d l5 1-14 ibib hitstr abs

L5   ANSWER 1 OF 14  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2003:438097  CAPLUS
TITLE:                   Fenofibrate inhibits angiogenesis in vitro
                         and in vivo
AUTHOR(S):               Varet, J.; Vincent, L.; Mirshahi, P.; Pille, J.-V.;
                         Legrand, E.; Opolon, P.; Mishal, Z.; Soria, J.; Li,
                         H.; Soria, C.
CORPORATE SOURCE:        Laboratoire DIFEMA, Faculte de Medecine et Pharmacie,
                         Rouen, 76183, Fr.
SOURCE:                  Cellular and Molecular Life Sciences (2003), 60(4),
                         810-819
                         CODEN: CMLSFI; ISSN: 1420-682X
PUBLISHER:               Birkhaeuser Verlag
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Fenofibrate, a peroxisome proliferator-activated receptor (PPAR
     )-alpha activator, used as a normolipidemic agent, is thought to offer
     addnl. beneficial effects in atherosclerosis.  Since angiogenesis
     is involved in plaque progression, hemorrhage, and instability, the main
     causes of ischemic events, this study was designed to evaluate the action
     of fenofibrate on angiogenesis.  Our results show that
     fenofibrate.  (i) inhibits endothelial cell proliferation induced by
     angiogenic factors, followed at high concns. by an increase in apoptosis,.
     (ii) inhibits endothelial cell migration in a healing wound model,.  (iii)
     inhibits capillary tube formation in vitro, and.  (iv) inhibits
     angiogenesis in vivo.  Concerning the mechanism of action, the
     inhibition of endothelial cell migration by fenofibrate can be
     explained by a disorganization of the actin cytoskeleton.  At the mol.
     level, fenofibrate markedly decreased basic fibroblast growth
     factor-induced Akt activation and cyclooxygenase 2 gene expression.  This
     inhibition of angiogenesis could participate in the
```

beneficial effect of fenofibrate in atherosclerosis.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:308749 CAPLUS
TITLE: Current strategies for anticancer chemoprevention and chemoprotection
AUTHOR(S): Krzystyniak, Krzysztof L.
CORPORATE SOURCE: Department of Biological Sciences, University of Quebec-Montreal, Montreal, QC, H3C 3P8, Can.
SOURCE: Acta Poloniae Pharmaceutica (2002), 59(6), 473-478
CODEN: APPHAX; ISSN: 0001-6837
PUBLISHER: Polish Pharmaceutical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Relatively new targets in drug design projects in cancer pharmacol. include cytostatic agents, immune system modulators, and **angiogenesis** inhibitors. Preventive oncol. applies pharmacol. agents to reverse, retard, or halt progression of neoplastic cells to invasive malignancy. Prevention of cancer, however, can be accomplished through many strategies, including changes in diet and lifestyle. For example, the vast majority of lung cancers (80-90%) can be attributed to cigarette smoking and therefore, the most effective primary preventive strategy for lung cancer is to quit smoking. Chemoprevention through interruption of multistage carcinogenesis include different mol. targets. Selective estrogen receptor modulators (SERMs) act as estrogen receptor (ER) agonists. Ligands for the peroxisome proliferator-activated receptor gamma (**PPAR**-gamma) suppress breast carcinogenesis in exptl. models and induce differentiation of human liposarcoma cells. Selective **PPAR** modulators (SPARMs), by analogy to the SERM concept, are designed to have desired effects on specific genes relevant to carcinogenesis. Enzymic approach in endocrine-related tumors involve **inhibition** of aromatase to prevent breast cancer and **inhibition** of 5-alpha-reductase to prevent prostate cancer. Down-regulation of inflammatory prostaglandin synthesis by **inhibition** of cyclooxygenase -2 (COX-2), **inhibition** of the inducible nitric oxide synthase (iNOS), and stimulation of phase II detoxication system, are currently examd. in exptl. models and clin. trials. Overall, potential targets in preventive strategies to reduce the risk of cancer involve agonists of endocrine receptors, factors down-regulating inflammation, factors inducing programmed cell death (PCD)/apoptosis, enzymic inhibitors and gene therapy.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:288778 CAPLUS
TITLE: **PPAR** gamma, leptin and endothelial cell - mediated **angiogenesis**
AUTHOR(S): Polus, A.; Piatkowska, E.; Grzybowska, J.; Dembinska-Kiec, A.
CORPORATE SOURCE: Department of Clinical Biochemistry, Collegium Medicum Jagiellonian University, Krakow, Pol.
SOURCE: Atherosclerosis: Risk Factors, Diagnosis, and Treatment, [European Atherosclerosis Society Annual Congress], 73rd, Salzburg, Austria, July 7-10, 2002

(2002), 71-76. Editor(s): Kostner, Gert M.; Kostner, Karam M. Monduzzi Editore: Bologna, Italy.
CODEN: 69DTGD; ISBN: 88-323-2707-4
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Expressed on the neighborough cells proteins Notch and its ligand Jagged interactions are highly conserved mechanism that regulates cell fate decisions. The Jagged/Notch interaction by **inhibition** of cell differentiation may inhibit the **angiogenesis**. The homeobox (Hox) morphoregulatory genes encode transcription factors that play an essential role in organogenesis. HoxD3 promotes the invasive or migratory behavior when HoxB3 is required for capillary formation. **PPAR** .gamma. are the members of the steroid-receptor superfamily and are ligand-activated transcription factor which can regulate differentiation many type of cells. The aim of the study was to compare the influence VEGF, bFGF, leptin and the **PPAR**.gamma. activator on Jagged and Notch genes expression. Activators of **PPAR**.gamma. inhibit expression of Jagged/Notch genes in human umbilical endothelial cells so as bFGF and leptin do but did not induce tube formation in **angiogenesis** model in vitro.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:39829 CAPLUS
DOCUMENT NUMBER: 138:382796
TITLE: Participation of Jagged/Notch gene expression in differentiation of endothelial cells
AUTHOR(S): Dembinska-Kiec, A.; Polus, A.; Piatkowska, E.
CORPORATE SOURCE: Department of Clinical Biochemistry, Jagiellonian University Medical College, Krakow, Pol.
SOURCE: Advances in Coronary Artery Disease, Proceedings of the International Congress on Coronary Artery Disease, 4th, Prague, Czech Republic, Oct. 21-24, 2001 (2001), 169-175. Editor(s): Lewis, Basil S. Monduzzi Editore: Bologna, Italy.
CODEN: 69DLNU; ISBN: 88-323-1121-6
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The Notch and Jagged gene encoded transmembrane proteins mediate cell/cell recognition and potently affect the vascular morphogenesis. Notch signaling may function as a general arbiter of cell fate, regulating differentiation potential, rate of proliferation and apoptosis. The ligation-dependent cleaved intracellular domain of the Notch receptor is believed to enter the nucleus and interact with transcription factors of the CSL family inhibiting the activity and/or expression of differentiation-inducing cell type specific bHLH transcription factors. The preserved Jagged/Notch interaction may thus inhibit **angiogenesis** by **inhibition** of cell differentiation. We have demonstrated that ciglitazone activator of **PPAR** gamma as well as bFGF but not VEGF attenuate expression of Jagged and Notch genes in human umbilical vein endothelial cells.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:811662 CAPLUS

DOCUMENT NUMBER: 138:104914
TITLE: Leptin Induces Endothelial Cell Migration Through Akt, Which Is Inhibited by **PPAR**.gamma.-Ligands
AUTHOR(S): Goetze, Stephan; Bungenstock, Anne; Czupalla, Cornelia; Eilers, Friedrich; Stawowy, Philipp; Kintscher, Ulrich; Spencer-Haensch, Chantel; Graf, Kristof; Nuernberg, Bernd; Law, Ronald E.; Fleck, Eckart; Graefe, Michael
CORPORATE SOURCE: Department of Medicine/Cardiology, German Heart Institute Berlin, Germany
SOURCE: Hypertension (2002), 40(5), 748-754
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Migration of endothelial cells (EC) is a key event in **angiogenesis** that contributes to neovascularization in diabetic vasculopathy. Leptin induces **angiogenesis** and is elevated in obesity and hyperinsulinemia. The antidiabetic thiazolidinediones (TZD) inhibit leptin gene expression and vascular smooth muscle cell migration through activation of the peroxisome proliferator-activated receptor-.gamma. (**PPAR**.gamma.). This study investigates the role of leptin in EC migration, the chemotactic signaling pathways involved, and the effects of the TZD-**PPAR**.gamma. ligands troglitazone (TRO) and ciglitazone (CIG) on EC migration. We demonstrate that leptin induces EC migration. Because activation of two signaling pathways, the phosphatidylinositol-3 kinase (PI3K), Akt, eNOS and the ERK1/2 MAPK pathway, is known to be involved in cell migration, we used the pharmacol. inhibitors wortmannin and PD98059 to det. if chemotactic signaling by leptin involves Akt or ERK1/2, resp. Both wortmannin and PD98059 significantly inhibited leptin-induced migration. Treatment with the TZD-**PPAR**.gamma.-ligands TRO and CIG significantly inhibited the chemotactic response toward leptin. Both **PPAR**.gamma.-ligands inhibited leptin-stimulated Akt and eNOS phosphorylation, but neither attenuated ERK 1/2 activation in response to leptin. The **inhibition** of Akt-phosphorylation was accompanied by a **PPAR**.gamma.-ligand-mediated upregulation of PTEN, a phosphatase that functions as a neg. regulator of PI3K Akt signaling. These expts. provide the first evidence that activation of Akt and ERK 1/2 are crucial events in leptin-mediated signal transduction leading to EC migration. Moreover, **inhibition** of leptin-directed migration by the **PPAR**.gamma.-ligands TRO and CIG through **inhibition** of Akt underscores their potential in the prevention of diabetes-assocd. complications.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:770733 CAPLUS
DOCUMENT NUMBER: 138:297212
TITLE: **PPAR**.gamma. ligands inhibit primary tumor growth and metastasis by inhibiting **angiogenesis**
AUTHOR(S): Panigrahy, Dipak; Singer, Samuel; Shen, Lucy Q.; Butterfield, Catherine E.; Freedman, Deborah A.; Chen, Emy J.; Moses, Marsha A.; Kilroy, Susan; Duensing, Stefan; Fletcher, Christopher; Fletcher, Jonathan A.;

Hlatky, Lynn; Hahnfeldt, Philip; Folkman, Judah; Kaipainen, Arja
CORPORATE SOURCE: Surgical Research Laboratory, Department of Surgery, Children's Hospital, Harvard Medical School, Boston, MA, USA
SOURCE: Journal of Clinical Investigation (2002), 110(7), 923-932
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several drugs approved for a variety of indications have been shown to exhibit antiangiogenic effects. Our study focuses on the **PPAR** .gamma. ligand rosiglitazone, a compd. widely used in the treatment of type 2 diabetes. We demonstrate, for the first time to our knowledge, that **PPAR**.gamma. is highly expressed in tumor endothelium and is activated by rosiglitazone in cultured endothelial cells. Furthermore, we show that rosiglitazone suppresses primary tumor growth and metastasis by both direct and indirect antiangiogenic effects. Rosiglitazone inhibits bovine capillary endothelial cell but not tumor cell proliferation at low doses in vitro and decreases VEGF prodn. by tumor cells. In our in vivo studies, rosiglitazone suppresses **angiogenesis** in the chick chorioallantoic membrane, in the avascular cornea, and in a variety of primary tumors. These results suggest that **PPAR**.gamma. ligands may be useful in treating angiogenic diseases such as cancer by inhibiting **angiogenesis**.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:716010 CAPLUS
DOCUMENT NUMBER: 137:242464
TITLE: Treatment of tumors with steroids that interrupt disturbances in Wnt signaling or provide an angiostatic effect
INVENTOR(S): Hagstroem, Tomas
PATENT ASSIGNEE(S): Swed.
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072003	A2	20020919	WO 2002-SE443	20020311
WO 2002072003	A3	20030220		

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: SE 2001-857 A 20010313
OTHER SOURCE(S): MARPAT 137:242464

AB The present invention relates to steroid derivs. for use as medicaments. More specifically, the invention also relates to the use of a steroid deriv. of 5-androstene-, 5-pregnenolone or corresponding satd. derivs. (androstane- or pregnane-) in the manuf. of a medicament for the treatment of a benign and/or malignant tumor, which medicament is capable of interrupting disturbances in Wnt-signaling, such as cell-cycle arrest in G1-phase, and/or providing an angiostatic effect. Examples of such steroid derivs. are .DELTA.-5-androstene-17.alpha.-ol, androstane-17.alpha.-ol, or pregnane-17.alpha.-ol derivs. In a further aspect, the invention relates to a method of producing a medicament for the treatment of a benign and/or malignant tumor and/or an inflammatory condition comprising the steps of contacting 5-androstane-3.beta..alpha.,17.alpha.-diol or androstane-3.beta..alpha.-diol, an enzyme and a sulfotransferase to provide 5-androstene-17.alpha.-ol-3.beta.-sulfate or corresponding androstane deriv. (17.alpha.-AEDS or 17-AADS); and mixing the 17.alpha.-AEDS or 17.alpha.-AADS so produced with a suitable carrier; whereby a medicament which is capable of acting as a ligand to peroxisome proliferator-activated receptor-.gamma. (**PPAR** .gamma.) is produced. Pharmaceutical compns. contg. the steroids plus other nuclear receptor ligands are also claimed.

L5 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:109296 CAPLUS
DOCUMENT NUMBER: 136:292412
TITLE: Many actions of cyclooxygenase-2 in cellular dynamics and in cancer
AUTHOR(S): Cao, Yang; Prescott, Stephen M.
CORPORATE SOURCE: Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Journal of Cellular Physiology (2002), 190(3), 279-286
CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Cyclooxygenase-2 (COX-2) is the inducible isoform of cyclooxygenase, the enzyme that catalyzes the rate-limiting step in prostaglandin synthesis from arachidonic acid. Various prostaglandins are produced in a cell type-specific manner, and they elicit cellular functions via signaling through G-protein coupled membrane receptors, and in some cases, through the nuclear receptor **PPAR**. COX-2 utilization of arachidonic acid also perturbs the level of intracellular free arachidonic acid and subsequently affects cellular functions. In a no. of cell and animal models, induction of COX-2 has been shown to promote cell growth, inhibit apoptosis and enhance cell motility and adhesion. The mechanisms behind these multiple actions of COX-2 are largely unknown. Compelling evidence from genetic and clin. studies indicates that COX-2 upregulation is a key step in carcinogenesis. Overexpression of COX-2 is sufficient to cause tumorigenesis in animal models and **inhibition** of the COX-2 pathway results in redn. in tumor incidence and progression. Therefore, the potential for application of nonsteroidal anti-inflammatory drugs as well as the recently developed COX-2 specific inhibitors in cancer clin. practice has drawn tremendous attention in the past few years. **Inhibition** of COX-2 promises to be an effective approach in the prevention and treatment of cancer,

esp. colorectal cancer.
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:16667 CAPLUS
DOCUMENT NUMBER: 137:103189
TITLE: COX-2 **inhibition** and prevention of cancer
AUTHOR(S): Giercksky, Karl-Erik
CORPORATE SOURCE: Department of Surgical Oncology, The University of Oslo, Oslo, Norway
SOURCE: Best Practice & Research, Clinical Gastroenterology (2001), 15(5), 821-833
CODEN: BPRCB6
PUBLISHER: Bailliere Tindall
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The potential for cyclooxygenase **inhibition** in cancer prevention and treatment is founded on epidemiol. (redn. of colorectal cancer in aspirin users), animal expts. and mol. genetics. Trials using the NSAID sulindac also reduced the no. of polyps in patients with familial adenomatous polyposis, but the well-known gastrointestinal toxic effects of aspirin and NSAIDs have discouraged the exploitation of their antineoplastic potential. The advent of specific COX-2 inhibitors, which do not interfere with the cytoprotective constitutive COX-1 enzyme, and the demonstration of increased COX-2 expression in many common malignancies beside colorectal cancer, has opened up new therapeutic possibilities. Recently a non-cyclooxygenase effect of COX-2 inhibitors, which combines the **PPAR**.delta. and the APC tumor suppressor activity, was also demonstrated. The selective COX-2 inhibitor celecoxib has been approved by the FDA for adjuvant treatment of familial adenomatous polyposis, and a large no. of prevention and treatment trials of colorectal and other common cancers (prostate and breast cancer) have been started.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:636609 CAPLUS
TITLE: Transcriptional activation of cyclooxygenase-2 (COX-2) can be blocked by natural substances
AUTHOR(S): Dannenberg, Andrew J.; Subbaramaiah, Kotha
CORPORATE SOURCE: Weill Medical College of Cornell University and Strang Cancer Prevention Center, New York, NY, 10021, USA
SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), AGFD-113. American Chemical Society: Washington, D. C.
CODEN: 69BUZP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB There are two isoforms of cyclooxygenase (COX), both of which catalyze the formation of prostaglandins (PGs) from arachidonic acid. COX-1 is a housekeeping gene that is expressed constitutively. COX-2, an immediate early response gene, is highly inducible by mitogenic and inflammatory stimuli. There is considerable evidence that COX-2 is important for tumorigenesis. COX-2 is overexpressed in transformed cells and in various

forms of cancer while levels of COX-1 remain essentially unchanged. Mice genetically engineered to be COX-2 deficient are protected against both intestinal and skin tumor formation. Moreover, newly developed selective inhibitors of COX-2 inhibit exptl. tumorigenesis. Several different mechanisms can potentially explain the link between COX-2 and cancer. PGs increase cell proliferation, promote **angiogenesis**, and inhibit immune surveillance, all of which favor the growth of malignant cells. Overexpression of COX-2 inhibits apoptosis and increases the invasiveness of malignant cells. In combination, these studies suggest that targeted **inhibition** of COX-2 is a promising approach to prevent cancer. Although chemopreventive strategies have focused on inhibitors of COX-2 enzyme activity, compds. that suppress the expression of COX-2 should also possess anti-cancer properties. Phenolic antioxidants (PA) and retinoic acid (RA) inhibit tumorigenesis. This prompted us to det. whether PA or RA inhibited phorbol ester (PMA)-mediated induction of COX-2 and PG synthesis. PA and RA suppressed PMA-mediated induction of COX-2 mRNA, protein and PG biosynthesis in human epithelial cells. Nuclear run-offs revealed increased rates of COX-2 transcription after treatment with PMA, an effect that was inhibited by PA and RA. PA inhibited PMA-mediated activation of protein kinase C (PKC) signaling which led, in turn, to suppression of COX-2 expression. In contrast, RA suppressed the transcriptional activation of COX-2 by antagonizing the AP-1 transcription factor complex. Importantly, these inhibitory effects are not unique to PA and RA. In two other recently completed studies, triterpenoids and ligands of **PPAR**.gamma. suppressed the transcriptional activation of COX-2. The detailed mechanisms by which natural substances inhibit COX-2 transcription vary. Nonetheless, these findings suggest that studies of diet-gene interactions should provide a mechanistic basis for developing healthier diets.

L5 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:337887 CAPLUS
DOCUMENT NUMBER: 135:132695
TITLE: Feedback control of arachidonate cascade in rheumatoid synoviocytes by 15-deoxy-.DELTA.12,14-prostaglandin J2
AUTHOR(S): Tsubouchi, Yasunori; Kawahito, Yutaka; Kohno, Masataka; Inoue, Ken-ichiro; Hla, Timothy; Sano, Hajime
CORPORATE SOURCE: First Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kawaramachi-hirokoji, Kamigyo-ku, Kyoto, 602-8566, Japan
SOURCE: Biochemical and Biophysical Research Communications (2001), 283(4), 750-755
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rheumatoid arthritis (RA) is a chronic polyarticular joint disease assocd. with massive synovial proliferation, inflammation, and **angiogenesis**. **PPAR**-.gamma. ligands, both 15-deoxy-.DELTA.12,14-prostaglandin J2 (15d- PGJ2) and troglitazone (TRO), can inhibit the growth of RA synoviocytes in vitro, and suppress the chronic inflammation of adjuvant-induced arthritis in rats, but the potency of 15d-PGJ2 is higher than TRO. Prostaglandin (PG) E2 plays important roles in joint erosion and synovial inflammation. In the present study, 15d-PGJ2, but not TRO and other prostanoids, suppressed

interleukin (IL)-1.beta.-induced PGE2 synthesis in rheumatoid synovial fibroblasts (RSFs) through the **inhibition** of cyclooxygenase (COX-2) and cytosolic phospholipase A2 (cPLA2) expression. Furthermore, the **inhibition** was not affected by pretreatment with anti-**PPAR**-.gamma. antibody. It means that this anti-inflammatory effect of 15d-PGJ2 for PG synthesis may be independent of **PPAR**-.gamma. and 15d-PGJ2 is a key regulator of neg. feedback of the arachidonate cascade on the COX pathway. These findings provide new insight into the feedback mechanism of the arachidonate cascade. (c) 2001 Academic Press.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:368081 CAPLUS
DOCUMENT NUMBER: 133:12750
TITLE: Method using a **PPAR**.gamma. ligand/agonist for inhibiting **angiogenesis** and treating tumor growth
INVENTOR(S): Gerritsen, Mary E.; Xin, Xiaohua E.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000030628	A2	20000602	WO 1999-US27612	19991118
WO 2000030628	A3	20011011		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1143953	A2	20011017	EP 1999-960538	19991118
EP 1143953	A3	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001036955	A1	20011101	US 2001-865859	20010525

PRIORITY APPLN. INFO.:
US 1998-109328P P 19981120
US 1999-116530P P 19990120
US 1999-443010 B1 19991117
WO 1999-US27612 W 19991118

OTHER SOURCE(S): MARPAT 133:12750

AB **Angiogenesis** is inhibited and the growth of tumors is treated by administering an effective amt. of a **PPAR**.gamma. ligand/agonist, optionally with an RXR receptor ligand.

L5 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:15004 CAPLUS

DOCUMENT NUMBER: 132:73666
TITLE: Ophthalmic uses of **PPAR**-.gamma. agonists and antagonists
INVENTOR(S): Pershadsingh, Harrihar A.; Levy, Daniel E.
PATENT ASSIGNEE(S): Photogenesis, Inc., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000194	A1	20000106	WO 1999-US14262	19990625
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9947134	A1	20000117	AU 1999-47134	19990625
US 6316465	B1	20011113	US 1999-342381	19990628

PRIORITY APPLN. INFO.: US 1998-90937P P 19980627
US 1998-90937 P 19980627
WO 1999-US14262 W 19990625

OTHER SOURCE(S): MARPAT 132:73666

AB Methods are disclosed for treating diseases of ocular tissues expressing the nuclear receptor **PPAR**-.gamma., by inhibiting the inflammatory response, the neovascularization and **angiogenesis**, and programmed cell death (apoptosis) in these target tissues, comprising administering to a human or animal in need of treatment an effective amt. of a compd. that modifies the activity of **PPAR**-.gamma., or a pharmaceutically acceptable salt or solvate thereof. Novel compds. and methods for their synthesis are provided.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:218899 CAPLUS
DOCUMENT NUMBER: 131:27714
TITLE: Peroxisome proliferator-activated receptor .gamma. ligands are potent inhibitors of **angiogenesis** in vitro and in vivo
AUTHOR(S): Xin, Xiaohua; Yang, Suya; Kowalski, Joe; Gerritsen, Mary E.
CORPORATE SOURCE: Department of Cardiovascular Research, Genentech, Inc., South San Francisco, CA, 94080, USA
SOURCE: Journal of Biological Chemistry (1999), 274(13), 9116-9121
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal

LANGUAGE: English
AB Peroxisome proliferator-activated receptor .gamma. (**PPAR**.gamma.) is a nuclear receptor that functions as a transcription factor to mediate ligand-dependent transcriptional regulation. Activation of **PPAR** .gamma. by the naturally occurring ligand, 15-deoxy-.DELTA.12,14-prostaglandin J2 (15d-PGJ2), or members of a new class of oral antidiabetic agents, e.g. BRL49653 and ciglitizone, has been linked to adipocyte differentiation, regulation of glucose homeostasis, **inhibition** of macrophage and monocyte activation, and **inhibition** of tumor cell proliferation. Here we report that human umbilical vein endothelial cells (HUVEC) express **PPAR**.gamma. mRNA and protein. Activation of **PPAR**.gamma. by the specific ligands 15d-PGJ2, BRL49653, or ciglitizone, dose dependently suppresses HUVEC differentiation into tube-like structures in three-dimensional collagen gels. In contrast, specific **PPAR**.alpha. and -.beta. ligands do not affect tube formation although mRNA for these receptors are expressed in HUVEC. **PPAR**.gamma. ligands also inhibit the proliferative response of HUVEC to exogenous growth factors. Treatment of HUVEC with 15d-PGJ2 also reduced mRNA levels of vascular endothelial cell growth factor receptors 1 (Flt-1) and 2 (Flk/KDR) and urokinase plasminogen activator and increased plasminogen activator inhibitor-1 (PAI-1) mRNA. Finally, administration of 15d-PGJ2 inhibited vascular endothelial cell growth factor-induced **angiogenesis** in the rat cornea. These observations demonstrate that **PPAR**.gamma. ligands are potent inhibitors of **angiogenesis** in vitro and in vivo, and suggest that **PPAR**.gamma. may be an important mol. target for the development of small-mol. inhibitors of **angiogenesis**.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 11:59:58 ON 24 JUN 2003)

FILE 'CAPLUS' ENTERED AT 12:00:11 ON 24 JUN 2003
L1 17499 S ANGIOGENESIS
L2 4010 S L1 AND INHIBITION
L3 0 S L2 AND (PPAR RECEPTOR)
L4 0 S L2AND PPAR
L5 14 S L2 AND PPAR

=> s l2 and englitazone
97 ENGLITAZONE
L6 2 L2 AND ENGLITAZONE

=> d l6 1-2 ibib hitstr abs

L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:368081 CAPLUS
DOCUMENT NUMBER: 133:12750
TITLE: Method using a PPAR.gamma. ligand/agonist for inhibiting **angiogenesis** and treating tumor growth
INVENTOR(S): Gerritsen, Mary E.; Xin, Xiaohua E.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000030628	A2	20000602	WO 1999-US27612	19991118
WO 2000030628	A3	20011011		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1143953	A2	20011017	EP 1999-960538	19991118
EP 1143953	A3	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001036955	A1	20011101	US 2001-865859	20010525

PRIORITY APPLN. INFO.:
US 1998-109328P P 19981120
US 1999-116530P P 19990120
US 1999-443010 B1 19991117
WO 1999-US27612 W 19991118

OTHER SOURCE(S): MARPAT 133:12750

AB **Angiogenesis** is inhibited and the growth of tumors is treated by administering an effective amt. of a PPAR.gamma. ligand/agonist, optionally with an RXR receptor ligand.

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:15004 CAPLUS
DOCUMENT NUMBER: 132:73666
TITLE: Ophthalmic uses of PPAR-.gamma. agonists and antagonists
INVENTOR(S): Pershadsingh, Harrihar A.; Levy, Daniel E.
PATENT ASSIGNEE(S): Photogenesis, Inc., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000194	A1	20000106	WO 1999-US14262	19990625
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,				

ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9947134	A1	20000117	AU 1999-47134		19990625
US 6316465	B1	20011113	US 1999-342381		19990628
PRIORITY APPLN. INFO.:			US 1998-90937P	P	19980627
			US 1998-90937	P	19980627
			WO 1999-US14262	W	19990625

OTHER SOURCE(S): MARPAT 132:73666

AB Methods are disclosed for treating diseases of ocular tissues expressing the nuclear receptor PPAR-.gamma., by inhibiting the inflammatory response, the neovascularization and **angiogenesis**, and programmed cell death (apoptosis) in these target tissues, comprising administering to a human or animal in need of treatment an effective amt. of a compd. that modifies the activity of PPAR-.gamma., or a pharmaceutically acceptable salt or solvate thereof. Novel compds. and methods for their synthesis are provided.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l2 and troglitazone
1199 TROGLITAZONE
L7 8 L2 AND TROGLITAZONE

=> d l7 1-7 ibib hitstr abs

L7 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:811662 CAPLUS
DOCUMENT NUMBER: 138:104914
TITLE: Leptin Induces Endothelial Cell Migration Through Akt, Which Is Inhibited by PPAR.gamma.-Ligands
AUTHOR(S): Goetze, Stephan; Bungenstock, Anne; Czupalla, Cornelia; Eilers, Friedrich; Stawowy, Philipp; Kintscher, Ulrich; Spencer-Haensch, Chantel; Graf, Kristof; Nuernberg, Bernd; Law, Ronald E.; Fleck, Eckart; Graefe, Michael
CORPORATE SOURCE: Department of Medicine/Cardiology, German Heart Institute Berlin, Germany
SOURCE: Hypertension (2002), 40(5), 748-754
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Migration of endothelial cells (EC) is a key event in **angiogenesis** that contributes to neovascularization in diabetic vasculopathy. Leptin induces **angiogenesis** and is elevated in obesity and hyperinsulinemia. The antidiabetic thiazolidinediones (TZD) inhibit leptin gene expression and vascular smooth muscle cell migration through activation of the peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.). This study investigates the role of leptin in EC migration, the chemotactic signaling pathways involved, and the effects of the TZD-PPAR.gamma. ligands **troglitazone** (TRO) and ciglitazone (CIG) on EC migration. We demonstrate that leptin induces EC migration. Because activation of two signaling pathways, the phosphatidylinositol-3 kinase (PI3K), Akt, eNOS and the ERK1/2 MAPK pathway, is known to be involved in cell migration, we used the pharmacol. inhibitors wortmannin and PD98059 to det. if chemotactic signaling by leptin involves Akt or

ERK1/2, resp. Both wortmannin and PD98059 significantly inhibited leptin-induced migration. Treatment with the TZD-PPAR.gamma.-ligands TRO and CIG significantly inhibited the chemotactic response toward leptin. Both PPAR.gamma.-ligands inhibited leptin-stimulated Akt and eNOS phosphorylation, but neither attenuated ERK 1/2 activation in response to leptin. The **inhibition** of Akt-phosphorylation was accompanied by a PPAR.gamma.-ligand-mediated upregulation of PTEN, a phosphatase that functions as a neg. regulator of PI3K Akt signaling. These expts. provide the first evidence that activation of Akt and ERK 1/2 are crucial events in leptin-mediated signal transduction leading to EC migration. Moreover, **inhibition** of leptin-directed migration by the PPAR.gamma.-ligands TRO and CIG through **inhibition** of Akt underscores their potential in the prevention of diabetes-assocd. complications.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:770733 CAPLUS
DOCUMENT NUMBER: 138:297212
TITLE: PPAR.gamma. ligands inhibit primary tumor growth and metastasis by inhibiting **angiogenesis**
AUTHOR(S): Panigrahy, Dipak; Singer, Samuel; Shen, Lucy Q.; Butterfield, Catherine E.; Freedman, Deborah A.; Chen, Emy J.; Moses, Marsha A.; Kilroy, Susan; Duensing, Stefan; Fletcher, Christopher; Fletcher, Jonathan A.; Hlatky, Lynn; Hahnfeldt, Philip; Folkman, Judah; Kaipainen, Arja
CORPORATE SOURCE: Surgical Research Laboratory, Department of Surgery, Children's Hospital, Harvard Medical School, Boston, MA, USA
SOURCE: Journal of Clinical Investigation (2002), 110(7), 923-932
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Several drugs approved for a variety of indications have been shown to exhibit antiangiogenic effects. Our study focuses on the PPAR.gamma. ligand rosiglitazone, a compd. widely used in the treatment of type 2 diabetes. We demonstrate, for the first time to our knowledge, that PPAR.gamma. is highly expressed in tumor endothelium and is activated by rosiglitazone in cultured endothelial cells. Furthermore, we show that rosiglitazone suppresses primary tumor growth and metastasis by both direct and indirect antiangiogenic effects. Rosiglitazone inhibits bovine capillary endothelial cell but not tumor cell proliferation at low doses in vitro and decreases VEGF prodn. by tumor cells. In our in vivo studies, rosiglitazone suppresses **angiogenesis** in the chick chorioallantoic membrane, in the avascular cornea, and in a variety of primary tumors. These results suggest that PPAR.gamma. ligands may be useful in treating angiogenic diseases such as cancer by inhibiting **angiogenesis**.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:884254 CAPLUS
DOCUMENT NUMBER: 136:160858

09865859

TITLE: Top 200 medicines: can new actions be discovered through computer-aided prediction?
AUTHOR(S): Poroikov, V.; Akimov, D.; Shabelnikova, E.; Filimonov, D.
CORPORATE SOURCE: Institute of Biomedical Chemistry of the Russian Academy of Medical Sciences, Moscow, 119832, Russia
SOURCE: SAR and QSAR in Environmental Research (2001), 12(4), 327-344
CODEN: SQERED; ISSN: 1062-936X
PUBLISHER: Gordon & Breach Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Computer-aided prediction of the biol. activity spectra by the program PASS was applied to a set of 130 pharmaceuticals from the list of the Top 200 medicines. The known pharmacol. effects were found in the predicted activity spectra in 93.2% of cases. Addnl., the probability of some supplementary effects was also predicted to be significant, including **angiogenesis inhibition**, bone formation stimulation, possible use in cognition disorders treatment, multiple sclerosis treatment, etc. These predictions, if confirmed exptl., may become a cause for a new application of pharmaceuticals from the Top 200 list. Most of known side and toxic effects were also predicted by PASS. PASS predictions at earlier R & D stages may thus provide a basis for finding new "leads" among already launched drugs and may help direct more attention to those particular effects of pharmaceuticals in clin. use which become apparent only in a small part of the population and require addnl. precautions.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:394831 CAPLUS
DOCUMENT NUMBER: 136:161068
TITLE: Response of experimental retinal neovascularization to thiazolidinediones
AUTHOR(S): Murata, Toshinori; Hata, Yasuaki; Ishibashi, Tatsuro; Kim, Sarah; Hsueh, Willa A.; Law, Ronald E.; Hinton, David R.
CORPORATE SOURCE: Department of Ophthalmology, Keck Sch. Med., University of Southern California, Los Angeles, CA, USA
SOURCE: Archives of Ophthalmology (Chicago, IL, United States) (2001), 119(5), 709-717
CODEN: AROPAW; ISSN: 0003-9950
PUBLISHER: American Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To det. the effect of thiazolidinediones (TZDs) on exptl. retinal neovascularization. The ability of the TZDs **troglitazone** and rosiglitazone maleate (1-20 .mu.mol/L) to inhibit retinal endothelial cell (REC) proliferation, migration, tube formation, and signaling was detd. in response to vascular endothelial growth factor (VEGF). In vivo studies were performed using the oxygen-induced ischemia model of retinal neovascularization. Neonatal mice were treated with intravitreous injection of 0.5 .mu.L of **troglitazone** (100 .mu.mol/L) or rosiglitazone maleate (100 .mu.mol/L), or vehicle, and retinal neovascularization was assayed qual. and quant. by angiog. and histol.

examn. Expression of the TZD receptor, peroxisome proliferator-activated receptor .gamma., was confirmed in RECs by Western immunoblotting. Rosiglitazone and **troglitazone** inhibited VEGF-induced migration, proliferation, and tube formation by RECs in vitro beginning at 10 .mu.mol/L. Rosiglitazone and **troglitazone** inhibited phosphorylation of extracellular signal-regulated mitogen-activated protein kinase 1 in RECs. Intravitreous injection of rosiglitazone or **troglitazone** inhibited development of retinal neovascularization but did not significantly inhibit VEGF overexpression in the ganglion cell layer of the ischemic retina. The TZDs inhibit exptl. retinal neovascularization with an effect that is primarily downstream of VEGF expression. The TZDs are widely prescribed and should be evaluated for their potential to inhibit the progression of diabetic retinopathy.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:337887 CAPLUS
DOCUMENT NUMBER: 135:132695
TITLE: Feedback control of arachidonate cascade in rheumatoid synoviocytes by 15-deoxy-.DELTA.12,14-prostaglandin J2
AUTHOR(S): Tsubouchi, Yasunori; Kawahito, Yutaka; Kohno, Masataka; Inoue, Ken-ichiro; Hla, Timothy; Sano, Hajime
CORPORATE SOURCE: First Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kawaramachi-hirokoji, Kamigyo-ku, Kyoto, 602-8566, Japan
SOURCE: Biochemical and Biophysical Research Communications (2001), 283(4), 750-755
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rheumatoid arthritis (RA) is a chronic polyarticular joint disease assocd. with massive synovial proliferation, inflammation, and **angiogenesis**. PPAR-.gamma. ligands, both 15-deoxy-.DELTA.12,14-prostaglandin J2 (15d- PGJ2) and **troglitazone** (TRO), can inhibit the growth of RA synoviocytes in vitro, and suppress the chronic inflammation of adjuvant-induced arthritis in rats, but the potency of 15d-PGJ2 is higher than TRO. Prostaglandin (PG) E2 plays important roles in joint erosion and synovial inflammation. In the present study, 15d-PGJ2, but not TRO and other prostanoids, suppressed interleukin (IL)-1.beta.-induced PGE2 synthesis in rheumatoid synovial fibroblasts (RSFs) through the **inhibition** of cyclooxygenase (COX-2) and cytosolic phospholipase A2 (cPLA2) expression. Furthermore, the **inhibition** was not affected by pretreatment with anti-PPAR-.gamma. antibody. It means that this anti-inflammatory effect of 15d-PGJ2 for PG synthesis may be independent of PPAR-.gamma. and 15d-PGJ2 is a key regulator of neg. feedback of the arachidonate cascade on the COX pathway. These findings provide new insight into the feedback mechanism of the arachidonate cascade. (c) 2001 Academic Press.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:400583 CAPLUS

DOCUMENT NUMBER: 133:115515
TITLE: Dissociation between the Ca2+ signal and tube formation induced by vascular endothelial growth factor in bovine aortic endothelial cells
AUTHOR(S): Kawasaki, J.; Hirano, K.; Hirano, M.; Nishimura, J.; Nakatsuka, A.; Fujishima, M.; Kanaide, H.
CORPORATE SOURCE: Graduate School of Medical Sciences, Research Institute of Angiocardiology, Department of Molecular Cardiology, Kyushu University, Fukuoka, 812-8582, Japan
SOURCE: European Journal of Pharmacology (2000), 398(1), 19-29
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The correlation between the intracellular Ca2+ signal and the tube formation in collagen gels induced by vascular endothelial cell growth factor (VEGF) was investigated using cultured bovine aortic endothelial cells. The VEGF-induced sustained elevation of cytosolic Ca2+ concn. ([Ca2+]i) was similarly inhibited by 10 .mu.M SKF 96365 and 10 .mu.M **troglitazone**. However, 10 .mu.M diltiazem had no effect. The basal tube formation obtained with 1% serum was augmented twofold by 100 ng/mL VEGF. SKF 96365 (0.1-10 .mu.M) inhibited the VEGF-induced and basal tube formation, while 10 .mu.M **troglitazone** or 10 .mu.M diltiazem had no effect. The proliferation of endothelial cells was markedly inhibited by SKF 96365 but only slightly by **troglitazone** and diltiazem. The **inhibition** of tube formation by three Ca2+ entry blockers thus correlated with the **inhibition** of cell proliferation. The [Ca2+]i elevation is thus not a prerequisite for VEGF to induce tube formation.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:368081 CAPLUS
DOCUMENT NUMBER: 133:12750
TITLE: Method using a PPAR.gamma. ligand/agonist for inhibiting **angiogenesis** and treating tumor growth
INVENTOR(S): Gerritsen, Mary E.; Xin, Xiaohua E.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000030628	A2	20000602	WO 1999-US27612	19991118
WO 2000030628	A3	20011011		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1143953	A2	20011017	EP 1999-960538	19991118
EP 1143953	A3	20020206		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

US 2001036955	A1	20011101	US 2001-865859	20010525

PRIORITY APPLN. INFO.:	US 1998-109328P	P	19981120
	US 1999-116530P	P	19990120
	US 1999-443010	B1	19991117
	WO 1999-US27612	W	19991118

OTHER SOURCE(S): MARPAT 133:12750

AB **Angiogenesis** is inhibited and the growth of tumors is treated by administering an effective amt. of a PPAR.gamma. ligand/agonist, optionally with an RXR receptor ligand.

=> s l2 and ciglitazone
288 CIGLITAZONE
L8 5 L2 AND CIGLITAZONE

=> d l8 1-5 ibib hitstr abs

L8 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:39829 CAPLUS
DOCUMENT NUMBER: 138:382796
TITLE: Participation of Jagged/Notch gene expression in differentiation of endothelial cells
AUTHOR(S): Dembinska-Kiec, A.; Polus, A.; Piatkowska, E.
CORPORATE SOURCE: Department of Clinical Biochemistry, Jagiellonian University Medical College, Krakow, Pol.
SOURCE: Advances in Coronary Artery Disease, Proceedings of the International Congress on Coronary Artery Disease, 4th, Prague, Czech Republic, Oct. 21-24, 2001 (2001), 169-175. Editor(s): Lewis, Basil S. Monduzzi Editore: Bologna, Italy.
CODEN: 69DLNU; ISBN: 88-323-1121-6
DOCUMENT TYPE: Conference
LANGUAGE: English

AB The Notch and Jagged gene encoded transmembrane proteins mediate cell/cell recognition and potently affect the vascular morphogenesis. Notch signaling may function as a general arbiter of cell fate, regulating differentiation potential, rate of proliferation and apoptosis. The ligation-dependent cleaved intracellular domain of the Notch receptor is believed to enter the nucleus and interact with transcription factors of the CSL family inhibiting the activity and/or expression of differentiation-inducing cell type specific bHLH transcription factors. The preserved Jagged/Notch interaction may thus inhibit **angiogenesis** by **inhibition** of cell differentiation. We have demonstrated that **ciglitazone** activator of PPAR gamma as well as bFGF but not VEGF attenuate expression of Jagged and Notch genes in human umbilical vein endothelial cells.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:811662 CAPLUS
DOCUMENT NUMBER: 138:104914
TITLE: Leptin Induces Endothelial Cell Migration Through Akt, Which Is Inhibited by PPAR.gamma.-Ligands
AUTHOR(S): Goetze, Stephan; Bungenstock, Anne; Czupalla, Cornelia; Eilers, Friedrich; Stawowy, Philipp; Kintscher, Ulrich; Spencer-Haensch, Chantel; Graf, Kristof; Nuernberg, Bernd; Law, Ronald E.; Fleck, Eckart; Graefe, Michael
CORPORATE SOURCE: Department of Medicine/Cardiology, German Heart Institute Berlin, Germany
SOURCE: Hypertension (2002), 40(5), 748-754
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Migration of endothelial cells (EC) is a key event in **angiogenesis** that contributes to neovascularization in diabetic vasculopathy. Leptin induces **angiogenesis** and is elevated in obesity and hyperinsulinemia. The antidiabetic thiazolidinediones (TZD) inhibit leptin gene expression and vascular smooth muscle cell migration through activation of the peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.). This study investigates the role of leptin in EC migration, the chemotactic signaling pathways involved, and the effects of the TZD-PPAR.gamma. ligands troglitazone (TRO) and **ciglitazone** (CIG) on EC migration. We demonstrate that leptin induces EC migration. Because activation of two signaling pathways, the phosphatidylinositol-3 kinase (PI3K), Akt, eNOS and the ERK1/2 MAPK pathway, is known to be involved in cell migration, we used the pharmacol. inhibitors wortmannin and PD98059 to det. if chemotactic signaling by leptin involves Akt or ERK1/2, resp. Both wortmannin and PD98059 significantly inhibited leptin-induced migration. Treatment with the TZD-PPAR.gamma.-ligands TRO and CIG significantly inhibited the chemotactic response toward leptin. Both PPAR.gamma.-ligands inhibited leptin-stimulated Akt and eNOS phosphorylation, but neither attenuated ERK 1/2 activation in response to leptin. The **inhibition** of Akt-phosphorylation was accompanied by a PPAR.gamma.-ligand-mediated upregulation of PTEN, a phosphatase that functions as a neg. regulator of PI3K Akt signaling. These expts. provide the first evidence that activation of Akt and ERK 1/2 are crucial events in leptin-mediated signal transduction leading to EC migration. Moreover, **inhibition** of leptin-directed migration by the PPAR.gamma.-ligands TRO and CIG through **inhibition** of Akt underscores their potential in the prevention of diabetes-assocd. complications.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:368081 CAPLUS
DOCUMENT NUMBER: 133:12750
TITLE: Method using a PPAR.gamma. ligand/agonist for inhibiting **angiogenesis** and treating tumor growth
INVENTOR(S): Gerritsen, Mary E.; Xin, Xiaohua E.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000030628	A2	20000602	WO 1999-US27612	19991118
WO 2000030628	A3	20011011		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1143953	A2	20011017	EP 1999-960538	19991118
EP 1143953	A3	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2001036955	A1	20011101	US 2001-865859	20010525

PRIORITY APPLN. INFO.:
US 1998-109328P P 19981120
US 1999-116530P P 19990120
US 1999-443010 B1 19991117
WO 1999-US27612 W 19991118

OTHER SOURCE(S): MARPAT 133:12750

AB **Angiogenesis** is inhibited and the growth of tumors is treated by administering an effective amt. of a PPAR.gamma. ligand/agonist, optionally with an RXR receptor ligand.

L8 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:15004 CAPLUS
DOCUMENT NUMBER: 132:73666
TITLE: Ophthalmic uses of PPAR-.gamma. agonists and antagonists
INVENTOR(S): Pershadsingh, Harrihar A.; Levy, Daniel E.
PATENT ASSIGNEE(S): Photogenesis, Inc., USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000194	A1	20000106	WO 1999-US14262	19990625
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,				

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9947134	A1	20000117	AU 1999-47134	19990625
US 6316465	B1	20011113	US 1999-342381	19990628

PRIORITY APPLN. INFO.: US 1998-90937P P 19980627
US 1998-90937 P 19980627
WO 1999-US14262 W 19990625

OTHER SOURCE(S): MARPAT 132:73666

AB Methods are disclosed for treating diseases of ocular tissues expressing the nuclear receptor PPAR-.gamma., by inhibiting the inflammatory response, the neovascularization and **angiogenesis**, and programmed cell death (apoptosis) in these target tissues, comprising administering to a human or animal in need of treatment an effective amt. of a compd. that modifies the activity of PPAR-.gamma., or a pharmaceutically acceptable salt or solvate thereof. Novel compds. and methods for their synthesis are provided.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:218899 CAPLUS

DOCUMENT NUMBER: 131:27714

TITLE: Peroxisome proliferator-activated receptor .gamma. ligands are potent inhibitors of **angiogenesis** in vitro and in vivo

AUTHOR(S): Xin, Xiaohua; Yang, Suya; Kowalski, Joe; Gerritsen, Mary E.

CORPORATE SOURCE: Department of Cardiovascular Research, Genentech, Inc., South San Francisco, CA, 94080, USA

SOURCE: Journal of Biological Chemistry (1999), 274(13), 9116-9121
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Peroxisome proliferator-activated receptor .gamma. (PPAR.gamma.) is a nuclear receptor that functions as a transcription factor to mediate ligand-dependent transcriptional regulation. Activation of PPAR.gamma. by the naturally occurring ligand, 15-deoxy-.DELTA.12,14-prostaglandin J2 (15d-PGJ2), or members of a new class of oral antidiabetic agents, e.g. BRL49653 and ciglitizone, has been linked to adipocyte differentiation, regulation of glucose homeostasis, **inhibition** of macrophage and monocyte activation, and **inhibition** of tumor cell proliferation. Here we report that human umbilical vein endothelial cells (HUVEC) express PPAR.gamma. mRNA and protein. Activation of PPAR.gamma. by the specific ligands 15d-PGJ2, BRL49653, or ciglitizone, dose dependently suppresses HUVEC differentiation into tube-like structures in three-dimensional collagen gels. In contrast, specific PPAR.alpha. and -.beta. ligands do not affect tube formation although mRNA for these receptors are expressed in HUVEC. PPAR.gamma. ligands also inhibit the proliferative response of HUVEC to exogenous growth factors. Treatment of HUVEC with 15d-PGJ2 also reduced mRNA levels of vascular endothelial cell growth factor receptors 1 (Flt-1) and 2 (Flk/KDR) and urokinase plasminogen activator and increased plasminogen activator inhibitor-1 (PAI-1) mRNA. Finally, administration of 15d-PGJ2 inhibited vascular endothelial cell growth factor-induced **angiogenesis** in the rat cornea. These observations demonstrate that PPAR.gamma. ligands are potent inhibitors of **angiogenesis**

in vitro and in vivo, and suggest that PPAR.gamma. may be an important mol. target for the development of small-mol. inhibitors of **angiogenesis**.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> logoff
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:H

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	89.43	89.64

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-18.23	-18.23

SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 12:07:04 ON 24 JUN 2003